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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,788	05/25/2007	David T.W. Wong	02307K-159700US	2289

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
JANSSEN, SHANNON L	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,788	WONG ET AL.	
	Examiner	Art Unit	
	SHANNON JANSSEN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-13 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-13 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *Jul 13, 2007, Novr 14, 2007, Feb 27, 2008, Apr 16, 2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 10-13 and 28 are currently pending and under consideration. Claims 1-9 and 14-27 were canceled and claim 28 was added in the claim amendments received August 18, 2009. Please Note: the examiner of record has changed. Please address all future correspondence to the examiner listed at the conclusion of this action.

Election/Restrictions

Applicant's election of Group 5, claims 10-13, in the reply filed on August 18, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement regarding unity of invention, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's election of species of detecting a transcriptome, quantitative PCR, disease state, cancer of the oral cavity, and biomarker, IL-8, in the reply filed on August 18, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement regarding unity of invention, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Priority

The present application claims status as a National Stage entry of PCT/US05/05263, filed February 17, 2005. The present application also claims priority based on US Provisional application numbers 60/546507, filed on February 20, 2004 and 60/546521, filed on February 21, 2004.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on July 13, 2007, November 14, 2007, February 27, 2008, and April 16, 2010 are being considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-13 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of determining if breast cancer cells have an altered copy number at specific regions on chromosome 20, the specification does not provide sufficient guidance for diagnosing breast cancer. The specification does not enable a person skilled in the art to make and use the invention commensurate in scope with the claim. This is a **scope of enablement** rejection. Modifications to the rejection were necessitated by the claim amendments for clarification.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The level of skill in the art;
5. The level of predictability in the art;
6. The amount of direction provided by the inventor;
7. The presence or absence of working examples;
8. The quantity of experimentation necessary needed to make or use the invention based on the disclosure.

See *In re Wands* USPQ 2d 1400 (CAFC 1988):

The breadth of the claims and the nature of the invention:

The present invention is drawn to a method for diagnosing an oral or systemic pathology, disease, or disorder in a subject comprising detecting, in a cell free saliva fluid phase of a subject, an "mRNA profile" of a gene associated with the pathology, disease, or disorder, and comparing the RNA profile of the gene with a predetermined mRNA profile of the gene. The invention as claimed encompasses all known pathologies, diseases, and disorders and diagnosis of the disorder using any single gene.

Although addressing the method of correlating gene expression levels in subjects known to have the oral squamous cell carcinoma (OSCC), the specification does not provide sufficient guidance for diagnosing any cancer, or oral cancer, in an unknown sample. The specification also does not address diagnosing any cancer with a single gene. Specifically, the specification provides data regarding expression levels of select genes in subjects having OSCC compared to normal subjects, however the specification does not provide data regarding diagnosing an unknown subject, or using the gene expression levels to differentiate any unknown subjects, with any disease, from any other subjects. In fact, the specification provides no data regarding differentiating any subject with OSCC from any other subject using a single gene. There are no specific examples or data demonstrating diagnosis of any cancer, or any oral or head and neck cancer, by correlating with gene expression. The specification also provides no specific examples of diagnosing OSCC by correlating with gene expression of a single gene. The specification merely teaches correlating changes in gene expression form subjects known to have OSCC. Accordingly, the claim scope is unduly broad with respect to the encompassed method of

diagnosing an oral or systemic pathology, disease, or disorder in a subject, including oral cancer, OSCC, or head and neck cancer.

The state of the prior art and the level of predictability in the art:

Diagnosis of cancer (or oral cancer/OSCC) by correlating with gene expression is highly unpredictable in the art. Not all subjects have the same altered gene expression and have alterations in different genes. For example, Sun et al. (Gene expression profiling on lung cancer outcome prediction: present clinical value and future premise, 2006, Cancer Epidemiol Biomarkers Prev, Vol 15, pp 2063-2068) teach that while gene expression data and microarray analysis show promise as analytical tools, its clinical applications are still questionable (see p 2066, col 1, last para through col 2, first para). Sun et al. further list various issues that arise in application of microarray data in clinical settings:

> "Reasons include the following: (a) There is a significant overlap for clinical outcome prediction between gene expression profiles and pathologic features, and most studies have not shown a superior performance using the new technology over conventional predictors, particularly when evaluated collectively. (b) Most studies had a limited number of cases and an independent validation was not adequately conducted. (c) Current analytic algorithms favor genes at high expression or genes highly differentially expressed, most of which are related to tumor differentiation and may not correlate with clinical outcomes; conversely, genes expressed at low levels or in a subtle difference are often overlooked, which may be quite relevant biologically to clinical questions. (d) There are still some unsolved technical issues about DNA microarray; for example, different microarray platforms (27) or studies from different laboratories using the same platform (28) often produce inconsistent results even when the same RNA samples were used for hybridization. (e) Results from different analytic approaches also differ (23). As an undesirable consequence, consistent or overlapped genes selected for predicting the same outcome from multiple studies are rare." (See p 2067, para 1).

Ziober et al. (Lab-on-a-chip for oral cancer screening and diagnosis, 2008, Head and Neck, Vol 30, pp 111-121) also discuss gene expression analysis for diagnosis of cancer, and OSCC in particular, and state: "However, to date, no single gene has shown sufficient diagnostic

utility in OSCC. Thus, as in many other cancers, clinical diagnosis will require considering the combined influence of many genes" (emphasis added, see p 114, col 1, para 2). Ziober et al. go on to discuss the state of the art regarding the predictive power of expression profiles and their clinical usefulness:

> "Unfortunately, there are still many questions regarding the identification of various expression profiles, establishing their predictive power, and developing procedures to collect, process, and analyze specific cancer samples and derive clinically useful information utilizing these cancer markers. Synergism from coordinated development of practical lab-on-a-chip systems in parallel and close collaboration with supporting and exploratory biomedical and clinical research would foster progress in both microfluidics technology and cancer diagnostics and therapeutics" (see p 119, col 2, para 2).

Westra et al. (Toward early oral cancer detection using gene expression profiling of saliva: a thoroughfare or a dead end?, 2004, Clinical Cancer Research, Vol 10, pp 8130-8131) also discuss the problems with using gene expression analysis for diagnosis of cancer, particularly in regards to OSCC (throughout document). Westra et al. list some of the issues such as obtaining and validating markers are up-regulated in high-risk tissues, but not normal tissues, and that they must be altered in early stages in cancer development (see p 8130, col 1, para 1). Westra et al. further caution against the use of IL-8 as a specific biomarker of oral cancer because IL-8 levels increase in a variety of oral inflammatory conditions and state:

> "Second, the exclusivity of a gene expression profile for oral neoplasia must first be established before that particular profile is embraced as a "cancer signature." The background frequency of the biomarker must be documented for individuals without oral cancer across a broad range of exposures (*e.g.,* tobacco and alcohol) and nonneoplastic conditions (*e.g.,* dental caries and gingivitis). The enthusiasm for using interleukin (IL)-8, an inflammatory cytokine, as a specific biomarker of oral cancer must be tempered by an awareness that IL-8 levels also increase in a variety of oral inflammatory conditions (5, 6). IL-8 measurement has been advocated as an effective means of monitoring oral disease activity ranging from dental caries to chronic aphthous ulcers to (now) oral carcinoma. Ongoing population-based screening studies that seek to resolve cancer-

> specific alterations from the background clamor of extraneous variations will ultimately prove indispensable to a more deliberate interpretation of gene expression data. This uncompromising rejection of even a marginal false positive rate has been the downfall of many initially promising attempts to screen for oral cancer.
>
> Third, translational studies that focus on early cancer detection and cancer risk assessment cannot lose sight of oral premalignancies (*i.e.*, oral dysplasia and carcinoma *in situ*), not overt malignancies, as the optimal target of gene expression profiling. Because Li *et al.* (3) did not include premalignancies, effective application of their approach to the arena of oral cancer screening is intriguing but speculative. Cancer-specific expression profiles of clinically apparent carcinomas are diagnostically relevant only to the degree that they are consistently present and measurable in early (*i.e.*, preclinical) stages of tumor progression." (See p 8130, col 2, para 3-4).

Lastly, Squire et al. (Molecular cytogenetic analysis of head and neck sqaumous cell carcinoma: by comparative genomic hybridization, spectral karyotyping, and expression array analysis, 2002, Head and Neck, Vol 24, pp 874-887) teach that while IL-8 was significantly over-expressed in OSCC samples, it was only consistently over-expressed in 3 out of 6 samples (see p 879, col 2, para 2), indicating the variability in IL-8 expression in OSCC samples and the variability in detecting positive correlation using IL-8 expression alone.

Therefor, the level of predictability in the art is dependent on many factors, altered gene expression could correlate with many different diseases, and detection of cancer using a single marker is unreliable. Thus, it is highly unpredictable to use altered expression data for the purpose of specifically diagnosing cancer in any subject.

The level of skill in the art:

The level of skill would be high, most likely at the Ph.D. level.

The amount of direction provided by the inventor and the existence of working examples:

While the applicants provide evidence of increased IL-8 expression in OSCC subjects, these increased levels are not present in all of the subjects (see Fig 5A), and there is no indication

of how these changes, alone, would be correlated with diagnosing cancer, or OSCC, in an unknown sample. In addition, there are no working examples of correlating gene expression with any other pathology, disease, or disorder (other than OSCC). The specification only teaches that altered gene/protein expression occurs in some OSCC patients, but does not teach how any one of these could be used to diagnose OSCC, or any other disease, pathology, or disorder in an unknown sample. Therefore, applicants have not provided any data regarding a method of diagnosing OSCC, or any disease, pathology, or disorder.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

In light of the unpredictability surrounding the claimed subject matter, the undue breadth of the claimed invention's intended use, and the lack of adequate guidance, one wishing to practice the presently claimed invention would be unable to do so without engaging in undue experimentation. One wishing to practice the presently claimed invention would have to produce additional experiments to determine how (or if) changes in expression of a single gene could be used to specifically diagnose OSCC in an unknown sample and would have to perform an immeasurable number of experiments to determine how (or if) changes in a single gene could be used to diagnose any disease, pathology or disorder, including determining what potential genes would even be used.

Claims 10-13 and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 USC 112, first paragraph "Written Description" requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a **written description** rejection.

Claim 10 is drawn to a method for diagnosing an oral or systemic pathology, disease, or disorder in a subject comprising detecting, in a cell free saliva fluid phase of a subject, an "mRNA profile" of a gene associated with the pathology, disease, or disorder, and comparing the RNA profile of the gene with a predetermined mRNA profile of the gene. The invention as claimed encompasses all known pathologies, diseases, and disorders and diagnosis of the disorder using any single gene.

The instant specification addresses a few genes associated with a specific type of cancer, oral squamous cell carcinoma (OSCC; see Examples). The instant specification teaches that there is a correlation between the expression of a group of specific genes with OSCC. However, the claimed invention does not include the limitation that the pathology, disease, or disorder is OSCC or the particular combination of genes (or genes and proteins) disclosed in the specification. Furthermore, the specification does not teach how any one particular gene could diagnose any oral or systemic pathology, disease, or disorder. Therefore, one skilled in the relevant art would not reasonably conclude that the Applicants had possession of the invention as claimed.

See Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or

she was *in possession of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See page 1116.).

University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Additionally, Cf. University of Rochester v G.D. Searle & Co., Inc., Monsanto Company, Pharmacia Corporation, and Pfizer Inc., No. 03-1304, 2004 WL 260813 (Fed. Cir., Feb. 13, 2004) held that:

> *Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods.*

In the present instance, the specification discloses only limited examples that are not representative of the claimed genus of a “gene associated with the pathology, disease, or disorder” or a “disease, pathology, or disorder”; nor do the claims recite sufficient structural feature(s) which is(are) common to members of the genus sufficient to demonstrate possession of the genus. With the exception of correlating expression of select genes with OSCC as disclosed

by the specification, the skilled artisan cannot envision the claimed method of diagnosing a disease, pathology, or condition, including diagnosing OSCC with a single gene.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-13 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites the limitation "the RNA profile" in line 6 and "the saliva" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 28 recites the limitation "wherein detecting a transcriptome pattern is" in lns 1-2. There is insufficient antecedent basis for this limitation in the claim. Further, it is unclear how a transcriptome pattern can be obtained from an mRNA profile of a single gene.

Invention as Claimed

The present invention is drawn to a method comprising providing a cell-free fluid phase portion of the saliva of the subject, detecting in the provided cell-free saliva fluid phase portion an mRNA profile of a gene associated with the pathology, disease or disorder, and comparing the RNA profile of the gene with a predetermined mRNA profile of the gene, the predetermined mRNA profile of the gene being indicative of the presence of the pathology, disease, or disorder in the subject.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by Gocke et al. (US Patent 6511805, granted January 28, 2003).

Regarding present claim 10, Gocke et al. teach a method for diagnosing malignancy comprising providing a cell fee biological sample, such as saliva, detecting mRNA expression of a papillomavirus gene (i.e.: associated with the pathology, disease, or disorder), comparing it to a positive control containing the gene of interest (i.e.: a predetermined mRNA profile of the gene, the predetermined mRNA profile of the gene being indicative of the presence of the pathology, a, or disorder; see entire document, particularly col 5, lns 4-50, clms 1-48).

Therefore, the teachings of Gocke et al. anticipate present claim 10.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim10-13 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kopreski et al. (US Patent 6607898, filed August 31, 2000), Kopreski et al. (US Patent 6759217, filed September 28, 2001), and Squire et al. (Molecular cytogenetic analysis of head and neck sqaumous cell carcinoma: by comparative genomic hybridization, spectral karyotyping, and expression array analysis, 2002, Head and Neck, Vol 24, pp 874-887).

Regarding present claims 10, 13, and 28, Kopreski et al. (2000) teach a method for diagnosing cancer, such as head and neck cancer (see claims 1-6), comprising providing a cell free biological sample, such as saliva, detecting extracellular mRNA expression of a gene associated with cancer, such as hTR or hTERT(i.e.: associated with the pathology, disease, or disorder), comparing it to a positive control containing the gene of interest (i.e.: a predetermined mRNA profile of the gene, the predetermined mRNA profile of the gene being indicative of the presence of the pathology, a, or disorder; see entire document, particularly col 1, lns 63+, col 2, lns 1-55, col 3, lns 9-19, 33-50, 60+, col 4, col 6, lns 46-59, clms 1-30).

While Kopreski et al. (2000) teach a method for diagnosing a systemic disease such as cancer by extracting mRNA from cell free fluids such as saliva, Kopreski et al. (2000) do not specifically teach quantitative PCR.

Regarding present claims 10 and 28, Kopreski et al. (2001) also teach a method for diagnosing cancer comprising providing a cell fee biological sample, such as saliva, detecting extracellular mRNA expression of a gene, such as EGF, c-myc, and her-2/neu, and performing quantitative PCR to enable comparison of the amount of extracellular mRNA present in a sample to the range of amounts of mRNA present in populations with cancer, premalignancy, and populations without cancer (see entire document, particularly col 2, lns 30-64col 8, lns 25-35, col 12, lns 9-16).

While Kopreski et al. (2000) and Kopreski et al. (2001) teach a method for diagnosing a systemic disease such as cancer by extracting mRNA from cell free fluids such as saliva, Kopreski et al. (2000) and Kopreski et al. (2001) do not specifically teach cancer of the oral cavity or IL-8.

Regarding present claims 11-13, Squire et al. teach a method comprising analyzing gene expression in subjects suffering from head and neck squamous cell carcinoma (HNSCC) of the oral cavity in order to identify regions subject to alterations in gene expression, and further teach upregulation of IL-8 mRNA in HNSCC samples (see entire document, particularly abstract, p 876, col2, last para, p 877, col 1, para 1, p 879, col 2, para 2, Table 4).

Therefor it would have been obvious to one of skill in the art at the time of the invention to mRNA levels by quantitative PCR as taught by Kopreski et al. (2001) and to detect IL-8 levels in OSCC subjects as taught by Squire et al. in the method taught by Kopreski et al. (2000).

One would have been motivated to do so because Kopreski et al. (2001) teach that quantitative PCR can be used to detect mRNA levels and enables comparison to other populations with malignancy, premalignancy, or normal (see col 12, lns 9-16) in order to

diagnose cancer and because Squire et al. teach that HNSCC, which encompasses OSCC, is the sixth most common human neoplasm and has low long-term survival (see p 875, col 1, para 1).

One would have had a reasonable expectation for success because Kopreski et al. (2000) and Kopreski et al. (2001) are both directed to detecting extracellular mRNA in samples from subjects in order to diagnose cancer and because Squire et al. Squire et al. teach also teach correlating up-regulated genes with cancer tissue and that IL-8 was one of five genes consistently up-regulated in OSCC samples (see p 879, col 2, para 2).

Therefor the teachings of Kopreski et al. (2000), Kopreski et al. (2001), and Squire et al. renders the present invention *prima facie* obvious.

In addition, it would have been obvious to one skilled in the art to substitute one known element (i.e.: Quantitative PCR taught by Kopreski et al. (2001) and correlating OSCC with IL-8 as taught by Squire et al.) for another known element (i.e.: methods of detecting, type of cancer, and marker taught by Kopreski et al. (2000)) using known methods (i.e.: the methods taught by all the methods) with no change in their respective functions, and the substitution would have yielded the predictable results of screening for IL-8 in saliva of OSCC patients to one of ordinary skill in the art at the time of the invention. See *KSR International Co. v. Teleflex Inc.*, USPQ2d 1385 (U.S. 2007).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10, 13, and 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4, 7-12, 14, 15, 17, and 20 of copending Application No. 12/468766. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are directed to a method for diagnosing a systemic disease comprising obtaining an mRNA profile of a gene (or genes)

from a saliva sample of a subject and comparing it to a control (i.e.: predetermined mRNA profile) utilizing, e.g., RT-PCR or microarray.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim10 and 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, and 7-10 of copending Application No. 12/457347. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are directed to a method for diagnosing a systemic disease, such as oral cancer or cancer of the head and neck, comprising obtaining an mRNA profile of a gene (or genes) from a saliva sample of a subject and comparing it to a control (i.e.: predetermined mRNA profile) utilizing, e.g., RT-PCR or microarray.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Future Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHANNON JANSSEN whose telephone number is (571)270-1303. The examiner can normally be reached on Generally M-F 9:00AM-6:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Amber D. Steele/
Primary Examiner, Art Unit 1639

Shannon L Janssen
SLJ